General

Guideline Title

Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (part review of technology appraisal guidance 70).

Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Apr. 74 p. (Technology appraisal guidance; no. 251).

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Institute for Clinical Excellence (NICE). Guidance on the use of imatinib for chronic myeloid leukaemia. London (UK): National Institute for Clinical Excellence (NICE); 2003 Oct. 26 p. (Technology appraisal; no. 70).

Recommendations

Major Recommendations

This guidance should be read in conjunction with the following National Institute for Health and Clinical Excellence (NICE) guidance: NICE technology appraisal guidance 70 (TA70) Guidance on the use of imatinib for chronic myeloid leukaemia.

This guidance partially updates NICE technology appraisal guidance 70 (published October 2003).

For details see About this guidance .

- Standard-dose imatinib* is recommended as an option for the first-line treatment of adults with chronic phase Philadelphia-chromosome-positive chronic myeloid leukaemia (CML).
- Nilotinib is recommended as an option for the first-line treatment of adults with chronic phase Philadelphia-chromosome-positive CML if the manufacturer makes nilotinib available with the discount agreed as part of the patient access scheme.
- Dasatinib is not recommended for the first-line treatment of chronic phase Philadelphia-chromosome-positive CML.
- People currently receiving dasatinib that is not recommended according to the above statement should be able to continue treatment until they and their clinician consider it appropriate to stop.

*The summary of product characteristics (SPC) for imatinib states that the recommended dosage of imatinib is 400 mg per day for patients in chronic phase CML.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Philadelphia-chromosome-positive chronic myeloid leukemia (CML)

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Hematology

Internal Medicine

Oncology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the clinical effectiveness and cost-effectiveness of dasatinib, nilotinib and standard-dose imatinib in the first-line treatment of chronic myeloid leukemia

Target Population

Patients with Philadelphia-chromosome-positive chronic myeloid leukemia (CML) in chronic phase

Interventions and Practices Considered

1. Standard-dose imatinib
2. Nilotinib

Note: Dasatinib was considered but not recommended as first-line treatment of chronic myeloid leukemia.

Major Outcomes Considered

- Clinical effectiveness
  - Response rates – cytogenetic, molecular, and haematological
  - Event-free survival
  - Progression-free survival
  - Overall survival
  - Time to treatment failure
  - Adverse effects of treatment
  - Health-related quality of life
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Peninsula Technology Assessment Group (PenTAG), University of Exeter (see the "Availability of Companion Documents" field.)

Clinical Effectiveness

Identification of Studies

The search strategy comprised of the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers and manufacturer submissions
- Follow-up on mentions of potentially relevant on-going trials noted in previous NICE guidance on imatinib for chronic myeloid leukaemia (CML)

The main electronic databases of interest were: MEDLINE (Ovid); EMBASE; The Cochrane Library including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, Database of Abstracts of Reviews of Effects (DARE), National Health Service Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) databases; NRR (National Research Register); Web of Science (including Conference Proceedings Citation Index); Current Controlled Trials; Clinical Trials.gov; US Food and Drug Administration (FDA) website; European Medicines Agency (EMEA) website. These were searched from search end-date of the last technology appraisal report on this topic October 2002.

The searches were developed and implemented by a trained information specialist using the search strategy detailed in the technology appraisal by Thompson Coon and colleagues as the starting point (see Appendix 1 of the Assessment Report [see the "Availability of Companion Documents" field] for full search strategy). This strategy was reviewed by PenTAG including a clinical expert.

Relevant studies were identified in two stages using predefined inclusion and exclusion criteria (see Appendix 2 of the Assessment Report [see the "Availability of Companion Documents" field] for full research protocol). One reviewer examined all titles and abstracts, with two reviewers each examining approximately 50% each of all titles and abstracts (therefore all titles and abstracts were examined by at least two reviewers). Full texts

of any potentially relevant studies were obtained. The relevance of each paper was assessed independently by two reviewers and any discrepancies resolved by discussion.

Inclusion Criteria

For the review of clinical effectiveness, in the first instance, only systematic reviews of randomised controlled trials (RCTs) and RCTs were considered. However, if key outcomes of interest were not measured at all in the included RCTs the Assessment Group discussed whether extending the range of included studies to other study designs. Other study designs were not required after scrutiny of the included RCTs. The systematic reviews were used as a source for finding further studies and to compare with the Assessment Group's systematic review. Systematic reviews provided as part of manufacturers' submissions were treated in a similar manner.

Population: Adults with chronic phase CML, naïve to any treatment specifically directed against CML.

Interventions

- Dasatinib
- Nilotinib
- Imatinib (400 mg standard dose)

Each should be employed in accordance with the marketing authorisation and in the populations indicated in Section 2.6 of the Assessment Report (see the "Availability of Companion Documents" field), noting that CML without genetic mutation is outside the existing marketing authorisations.

Comparators

- Imatinib or nilotinib where the intervention is dasatinib; imatinib or dasatinib where the intervention is nilotinib; dasatinib or nilotinib, where the intervention is standard dose imatinib.

Outcomes: All potentially relevant outcomes in the included studies were considered, particularly those capturing:

- Response rates – cytogenetic, molecular and haematological
- Event-free survival
- Progression-free survival
- Time to progression
- Overall survival
- Time to treatment failure
- Adverse effects of treatment
- Health-related quality of life

Exclusion Criteria

Studies were excluded if they did not match the inclusion criteria, particularly:

- Non-randomised studies (except if agreed by PenTAG, in the absence of RCTs)
- Animal models
- Preclinical and biological studies
- Narrative reviews, editorials, opinions
- Non-English language papers
- Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality

Methods for Reviewing Effectiveness of Surrogate Outcome Measures

Identification of Studies

The search strategy comprised of the following main elements:

- Searching of electronic databases
- Scrutiny of bibliographies of retrieved papers and manufacturer submissions

The following databases were searched: MEDLINE (Ovid); EMBASE; The Cochrane Library (including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, DARE, NHS EED and HTA databases); NRR (National Research Register); Web of Science (including Conference Proceedings); Current Controlled Trials; Clinical Trials.gov; FDA website; EMEA website. These were searched from

search end-date of the last technology appraisal report on this topic October 2002.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria:

Population: Adults with chronic phase CML, naïve to any interferon (IFN) or tyrosine kinase inhibitor (TKI) treatment.

Interventions: Dasatinib or nilotinib or imatinib in accordance with the marketing authorisation.

Comparators: Any or none

Outcomes

Final Patient-relevant Outcomes

- Progression-free survival
- Overall all cause survival
- Health-related quality of life

Potential Surrogate Outcomes

- Complete cytogenetic response
- Major molecular response

Study design: Any observational or experimental study that reported the association between complete cytogenetic response and/or major molecular response AND any one of the above final patient-relevant outcomes.

The Assessment Group excluded conference abstracts, narrative reviews, editorials, opinion pieces, non English language papers, individual case studies.

Studies were selected in two stages. First, two reviewers examined all titles and abstracts. Second, full texts of any potentially relevant studies were obtained and relevance of each paper assessed independently by the same two reviewers according to the inclusion and exclusion criteria and any discrepancies resolved by discussion.

Cost-Effectiveness

The Assessment Group undertook a systematic literature search to identify economic evaluations of the therapies under investigation, which were carried out in line with the scope of the current assessment. Appendix 1 of the Assessment Report (see the "Availability of Companion Documents" field) outlines in detail the search strategy used and databases searched. Manufacturer submissions to NICE were reviewed to identify additional studies.

All titles and abstracts were examined. The relevance of each paper was assessed according to the inclusion and exclusion criteria. The review was carried out by two researchers.

Number of Source Documents

Clinical Effectiveness

Four studies met the inclusion criteria:

- Two clinical randomised controlled trials (RCTs) (13 publications)
- One systematic review (2 publications)
- One indirect comparison study (1 publication)

Additional Studies for Surrogate Outcomes

- Five studies met the inclusion criteria: (RCTs n = 2, cohort studies n = 3; publications n = 11).
- Six publications were included in the quantitative analysis.

Cost-Effectiveness

- No published full economic evaluations were included.
- Five conference abstracts met inclusion criteria.
- Two economic models were provided by manufacturers for dasatinib and nilotinib.
- The Assessment Group developed its own economic model.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Peninsula Technology Assessment Group (PenTAG), University of Exeter (see the "Availability of Companion Documents" field.)

Clinical Effectiveness

Data Extraction Strategy

Data were extracted by one reviewer using a standardised data extraction form and checked independently by a second reviewer. Disagreements were resolved by discussion, with involvement of a third reviewer if necessary. Data extraction forms for each included study are included in Appendix 3 of the Assessment Report (see the "Availability of Companion Documents" field).

Quality Assessment Strategy

The methodological quality of randomised controlled studies was assessed according to criteria specified by the Centre of Reviews and Dissemination (CRD). Quality was assessed by one reviewer and judgements were checked by a second. Any disagreement was resolved by discussion, with involvement of a third reviewer if necessary.

Internal Validity

The instrument sought to assess the following considerations:

- Was the assignment to the treatment groups really random?
- Was the treatment allocation concealed?
- Were the groups similar at baseline in terms of prognostic factors?
- Were the eligibility criteria specified?
- Were outcome assessors blinded to the treatment allocation?
- Was the care provider blinded?
- Was the patient blinded?
- Were point estimates and a measure of variability presented for the primary outcome measure?
- Did the analyses include an intention-to-treat (ITT) analysis?
- Were withdrawals and dropouts completely described?

In addition, methodological notes were made for each included study, with the reviewer's observation on: sample size and power calculations, participant attrition, methods of data analysis, and conflicts of interest.

External Validity

External validity was judged according to the ability of a reader to consider the applicability of findings to a patient group and service setting. Study findings can only be generalisable if they provide enough information to consider whether a cohort is representative of the affected population at large. Therefore studies that appeared to be typical of the UK chronic myeloid leukaemia (CML) population with regard to these considerations were judged to be externally valid.

Methods of Data Synthesis

Data were tabulated and discussed in a narrative review. Given the paucity of data, a meta-analysis was not conducted.

Mixed treatment indirect comparisons were used as far as data allowed to facilitate comparison between the drugs for which there are no head to head data for dasatinib and nilotinib. From the data provided from the included trials, indirect comparisons are based on raw unadjusted results in the form of unadjusted odds ratios. The indirect log odds ratio and corresponding variance were calculated using standard formulae presented in the appendix of Bucher and colleagues.

Assuming the sampling distribution of the log odds ratio to be normally distributed, the Wald method was used to construct 95% confidence intervals for the odds ratio and calculate the p-value. A fixed effect approach was used which assumes that the relative effect of the interventions is the same across the two study populations. To check this assumption the Assessment Group compared the baseline characteristics between trials. The participants were similar with respect to median age, the percentage of males, median time between diagnosis and randomisation, median white cell count and median platelet count. It was not possible to use more sophisticated methods (e.g. sensitivity analyses and sub-group analyses) to validate the assumption of similar relative effects since there was no access to the original data.

Methods for Reviewing Effectiveness of Surrogate Outcome Measures

Data Extraction Strategy

Study characteristics and surrogate/final outcome data were extracted by one reviewer using a standardised data extraction form and independently checked by a second. Data digitalization software (WinDIG Version 2.5) was used to extract data from Kaplan Meier survival curves. Disagreements were resolved by discussion, with involvement of a third reviewer if necessary. Data extraction forms for each included study are included in Appendix 4 of the Assessment Report (see the "Availability of Companion Documents" field).

Quality Assessment Strategy

The methodological quality of included studies was assessed according to a modified list of criteria specified by the Centre of Reviews and Dissemination (CRD). Quality was assessed by one reviewer and judgements were checked by a second.

Methods of Data Synthesis

An initial review of included studies revealed two key limitations. Firstly, there was a lack of data reported to assess the trial level association between tyrosine kinase inhibitor (TKI) treatment effects on complete cytogenetic response and TKI treatment effect on patient-relevant outcome. This would be needed for high level evidence of surrogacy. Secondly, there was no presentation of data of the association of complete cytogenetic response or major molecular response and health-related quality of life. It was therefore decided to focus on studies that reported overall survival and/or progression free survival stratified by either complete cytogenetic response or major molecular response.

For each study, levels of overall survival (OS) and progression-free survival (PFS) were extracted by response stratum at each year following trial recruitment (or randomisation) up to the latest follow up point reported. In most studies OS and PFS data were reported in Kaplan-Meier curves using landmark analysis to evaluate differences in the final patient-relevant outcomes between responder and non-responders. The landmark method determines each patient's response at a fixed time point, with survival estimates calculated from that time point and associated statistical tests being conditional on patients' landmark responses.* Note that in this method, patients who die before the landmark time point are excluded from the analysis.

*In the included papers, the survival probabilities were referred to the starting of the treatment rather than to the time of response.

See section 5 of the Assessment Report (see the "Availability of Companion Documents" field) for more information about methods for reviewing effectiveness of surrogate outcome measures.

Cost-Effectiveness

Dasatinib

The manufacturer uses a "time in state" (area under the curve) model extrapolating CML related survival and progression-free survival data. The health states represent the chronic phase, and accelerated/blast phases as well as death. Within the chronic phase patients may also be in first, second or third line treatment, while in the accelerated/blast phases they may be receiving either third line treatments or palliative care. Time is modelled in blocks of 1 month (see Figure 14 in the Assessment Report [see the "Availability of Companion Documents" field]).

The manufacturer has modelled one scenario with three different comparators. The interventions and sequence of treatments are summarised in Table 28 of the Assessment Report.

Nilotinib

The manufacturer uses a Markov approach to model the cost-effectiveness of nilotinib compared to the current standard of care (imatinib 400 mg daily). This model has nine states. Patients enter the model in the chronic phase. The model estimates when one treatment fails and hence the patient is switched to an alternative treatment. At the end of each cycle, patients have a probability of remaining on current treatment, progressing to an alternative treatment or dying (see Figure 15 in the Assessment Report [see the "Availability of Companion Documents" field]).

The manufacturer modelled two different scenarios to reflect the availability or not of second generation TKIs as second-line treatment. The interventions and sequence of treatment is summarised in Table 30 of the Assessment Report.

The model predicts that nilotinib is both more effective and less costly compared to imatinib (dominates), when followed by dasatinib as second-line treatment.

The Assessment Group Model

The Assessment Group presented their economic model with a range of deterministic scenario analyses, depending on key structural assumptions. The scenario analyses are presented in Table 33 of the Assessment Report (see the "Availability of Companion Documents" field).

The PenTAG cost-effectiveness model is a state-transition model with states for the main disease phases, and for the different possible treatments within the chronic phase. The three alternative methods used in this model for estimating cost-effectiveness are:

- Cumulative Survival method - in which overall survival is estimated as the cumulative result of the duration of successive treatments.
- Surrogate Survival method – in which overall survival is estimated from the 12-month treatment response, either using complete cytogenetic response (CCyR) or major molecular response (MMR).
- Simplified method – in which the per patient costs and benefits occurring after treatment with TKIs are assumed equal between treatment arms

See Sections 7 and 8 of the Assessment Report (see the "Availability of Companion Documents" field) for additional information on cost-effectiveness.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service

(NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Manufacturers' Submissions

Dasatinib

The manufacturer developed a 'time in state' (area under the curve) model to assess the cost- effectiveness of dasatinib (100 mg daily), nilotinib (600 mg daily) and standard-dose imatinib (400 mg daily) as first-line treatments for people with chronic myeloid leukaemia (CML). The analysis was conducted from a UK National Health Service (NHS) perspective using a 40-year time horizon. It was based on a starting age of 46 years until 86 years. Costs and benefits were discounted at an annual rate of 3.5%. The health states modelled as monthly cycles represented the chronic phase, advanced phases (accelerated or blast phase) and death. For people receiving first-line dasatinib, second-line treatment was nilotinib (800 mg daily). For people receiving first-line nilotinib (600 mg daily), second-line treatment was dasatinib. For people receiving first-line standard-dose imatinib, second-line treatment was split 50:50 between dasatinib (100 mg daily) and nilotinib (800 mg daily).

The cost-effectiveness results indicated that dasatinib was associated with 20.46 years of overall survival (10.64 quality adjusted life years [QALYs]) at a total cost of £498,217; imatinib was associated with 18.83 years of overall survival (9.89 QALYs) at a total cost of £478,293; and nilotinib was associated with 20.59 years of overall survival (10.70 QALYs) at a total cost of £506,613. The base-case incremental cost-effectiveness ratios (ICERs) were £26,305 per QALY gained for dasatinib compared with imatinib and £144,778 per QALY gained for nilotinib compared with dasatinib.

Nilotinib

The manufacturer developed a Markov model to assess the cost-effectiveness of nilotinib 600 mg daily compared with standard-dose imatinib as first-line treatments in people with chronic phase CML. The analysis was conducted from a UK NHS and Personal Social Services perspective using a lifetime horizon with costs and benefits discounted at 3.5%. People entered the model in the chronic phase. The model estimated when one tyrosine kinase inhibitor treatment would fail and therefore when the person would be switched to an alternative treatment.

Two different scenarios were modelled to reflect the availability of second generation tyrosine kinase inhibitors as second-line treatment. In the first scenario, which was the base-case analysis used by the manufacturer, second-line treatment consisted of dasatinib (100 mg daily) followed by stem cell transplant or hydroxyurea as third-line treatment. In the second scenario, second-line treatment consisted only of stem cell transplant or

hydroxyurea with no third-line treatment available.

The base-case cost-effectiveness results with dasatinib as second-line treatment indicated that nilotinib was associated with an overall survival of 13.54 years (10.40 QALYs) and a total cost of £217,373 and that imatinib was associated with an overall survival of 12.83 years (9.85 QALYs) and a total cost of £227,744. Therefore, imatinib was dominated by nilotinib. The cost-effectiveness results with stem cell transplant or hydroxyurea as second-line treatment indicated that nilotinib was associated with an overall survival of 11.38 years (8.71 QALYs) and a total cost of £170,643 and that imatinib was associated with an overall survival of 9.97 years (7.62 QALYs) and a total cost of £166,015. The resulting ICER for nilotinib compared with imatinib was £5908 per QALY gained.

Summary of Appraisal Committee's Key Conclusions

The Committee noted that the acquisition costs of dasatinib and nilotinib were in excess of £30,000 per person per year, and that the cost of standard-dose imatinib had recently increased to approximately £20,000 per person per year.

The Committee was aware that the ICERs for first-line nilotinib followed by imatinib compared with first-line imatinib followed by nilotinib were sensitive to a number of parameters, including assumptions about the dose intensity of nilotinib and the average time spent on second-line nilotinib or imatinib treatment.

The Committee noted that the cost-effectiveness of dasatinib was unaltered by changes to all input parameters in the deterministic sensitivity analyses.

The Committee acknowledged the wide variation in the cost-effectiveness results across the scenarios presented by the Assessment Group, which reflected the considerable structural uncertainty in the modelling of first-line tyrosine kinase inhibitors for CML.

The Committee noted that the ICER for first-line nilotinib followed by imatinib compared with first-line imatinib followed by nilotinib was £11,000 per QALY gained in the Assessment Group's model and that this was within the range normally considered a cost-effective use of NHS resources. The Committee noted that dasatinib was associated with fewer QALYs gained and was more costly than nilotinib in all scenarios and that the ICERs for dasatinib compared with standard-dose imatinib exceeded £200,000 per QALY gained.

See Sections 4.2 and 4.3 of the original guideline document for details of the economic analyses provided by the manufacturers, the Assessment Group comments, and the Appraisal Committee considerations.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered clinical and cost-effectiveness evidence and a review of this submission by the Assessment Group. For

clinical effectiveness, two randomised controlled trials were the main source of evidence. For cost-effectiveness, two manufacturer economic models and the Assessment Group model were considered.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukemia

Potential Harms

- The most common reported side effects with dasatinib are headache, pleural effusion, shortness of breath, cough, diarrhoea, nausea, vomiting, abdominal pain, skin rash, musculoskeletal pain, infections, haemorrhage, superficial oedema, fatigue, fever, neutropenia, thrombocytopenia and anaemia. The summary of product characteristics (SPC) states: "Dasatinib should be administered with caution to patients who have or may develop prolongation of the QT interval."
- The most common side effects with imatinib include nausea, vomiting, oedema (fluid retention), muscle cramps, skin rash, diarrhoea, abdominal pain, headache and fatigue. For full details of side effects and contraindications, see the SPC.
- The most common side effects with nilotinib include thrombocytopenia, neutropenia, anaemia, headache, nausea, constipation, diarrhoea, rash, pruritus, fatigue and increased blood levels of lipase and bilirubin. Nilotinib prolongs the QT interval and should be used with caution in people who have or may develop prolongation of the QT interval. For full details of side effects and contraindications, see the SPC.

For full details of side effects and contraindications, see the SPC.

Contraindications

Contraindications

For full details of side effects and contraindications, see the summary of product characteristics (SPC).

Qualifying Statements

Qualifying Statements

- This guidance represents the view of the National Institute for Health and Clinical Excellence (NICE) and was arrived at after careful consideration of the available evidence. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the National Health

Service (NHS) in England and Wales on implementing National Institute for Health and Clinical Excellence (NICE) technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

- The Department of Health and the manufacturer have agreed that nilotinib will be available to the NHS with a patient access scheme in which a discount is applied to all invoices. The level of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate the level of discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to the manufacturer's commercial operations team on 01276 698717 or Commercial.Team@novartis.com.
- NICE has developed a costing statement explaining the resource impact of this guidance.

Implementation Tools

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Apr. 74 p. (Technology appraisal guidance; no. 251).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2003 Oct (revised 2012 Apr)

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Clinical Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

Committee Members: Dr David Black, Director of Public Health, Derbyshire County Primary Care Trust; Dr Daniele Bryden, Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS Trust; Dr Andrew Burnett, Director for Health Improvement and Medical Director, NHS Barnet, London; David Chandler, Lay member; Dr Mary Cooke, Lecturer, School of Nursing, Midwifery and Social Work, University of Manchester; Dr Chris Cooper, General Practitioner, St John's Way Medical Centre, London; Professor Peter Crome, Consultant Geriatrician and Professor of Geriatric Medicine, Keele University; Dr Christine Davey, Research Adviser, North and East Yorkshire Alliance Research and Development Unit, York; Richard Devereaux-Phillips, Director, Public Policy and Advocacy NW Europe, BD, Oxford; Professor Rachel A Elliott, Lord Trent Professor of Medicines and Health, University of Nottingham; Dr Greg Fell, Consultant in Public Health, Bradford and Airedale Primary Care Trust; Dr Wasim Hanif, Consultant Physician and Honorary Senior Lecturer, University Hospital Birmingham; Dr Alan Haycox, Reader in Health Economics, University of Liverpool Management School; Dr Peter Jackson, Clinical Pharmacologist, University of Sheffield; Dr Janice Kohler, Senior Lecturer and Consultant in Paediatric Oncology, Southampton University Hospital Trust; Dr Andrea Manca, Health Economist and Senior Research Fellow, University of York; Henry Marsh, Consultant Neurosurgeon, St George's Hospital, London; Professor Gary McVeigh, Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital; Professor Katherine Payne, Professor of Health Economics, University of Manchester; Dr Danielle Preedy, Lay member; Dr Martin Price, Head of Outcomes Research, Janssen-Cilag, Buckinghamshire; Alan Rigby, Senior Lecturer and Chartered Statistician, University of Hull; Dr Peter Selby, Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust; Dr Surinder Sethi, Consultant in Public Health Medicine, North West Specialised Services Commissioning Team, Warrington; Professor Andrew Stevens, Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham; Dr John Stevens, Lecturer in Bayesian Statistics in Health Economics, School of Health and Related Research, Sheffield; Dr Matt Stevenson, Technical Director, School of Health and Related Research, University of Sheffield; Dr Judith Wardle, Lay member

Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Institute for Clinical Excellence (NICE). Guidance on the use of imatinib for chronic myeloid leukaemia. London (UK): National Institute for Clinical Excellence (NICE); 2003 Oct. 26 p. (Technology appraisal; no. 70).

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (part review of technology appraisal guidance 70). Costing statement. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Apr. 4 p. (Technology appraisal guidance; no. 251). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .
- Dasatinib, nilotinib, and standard dose imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses. Technology assessment report. Exeter (UK): Peninsula Technology Assessment Group (PenTAG), University of Exeter; 2011 Sep 6. 252 p. Electronic copies: Available in PDF from the NICE Web site .
- Dasatinib, nilotinib, and standard dose imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses. Technology assessment report appendices. Exeter (UK): Peninsula Technology Assessment Group (PenTAG), University of Exeter; 2011 Sep 6. 175 p. Electronic copies: Available in PDF from the NICE Web site .

Patient Resources

The following is available:

- Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia. Understanding NICE guidance. Information for people with chronic myeloid leukaemia, their families and carers, and the public. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Apr. 8 p. (Technology appraisal guidance; no. 251). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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